## REMARKS

Status of the claims

Claims 4, 17 and 21-23 are pending. Claims 4 and 17 are rejected. Claims 4 and 17 are amended. Claims 1-3, 5-16 and 18-20 were canceled previously and claims 21-23 are canceled herein. No new matter is added.

Claim amendment

Claims 4 and 17 have been amended to recite a kit comprising primer pairs with sequences of SEQ ID NOS: 1 and 3 and SEQ ID NOS: 2 and 3 and the primer pairs, respectively (pg. 7, ll. 13-15; pg. 11, ll. 8-9; pg. 21, Table 1).

The 35 U.S.C. §102(a) rejection

Claims 4 and 17 stand rejected under 35 U.S.C. §102(a) as being anticipated by **Song** *et al.* (AAPS PharmSci 2002; 4(4) article 29 (http//www.aapspharmaci.org), published October 2, 2002). Applicants respectfully traverse this rejection.

As suggested by the Examiner, Applicants submit declarations under 35 C.F.R. §1.132 herewith to overcome this rejection. Accordingly, Applicants respectfully request that the rejection of claims 4 and 17 under 35 U.S.C. §102(a) be withdrawn.

The 35 U.S.C. §103(a) rejections

Claim 17 is rejected under 35 U.S.C. §103(a) as being unpatentable over **Song** *et al.* (Clinical Pharmacology & Therapeutics, Vol. 71, No. 2, February 2002, p. P103, abstract WPIII-100) in view of **Hoffmeyer** *et al.* (PNAS, Vol. 97, No. 7, pp. 3473-3478, March 28, 2000), GenBank M14758 (GI: 187468, 3 December 1999) and **Okimoto** *et al.* (BioTechniques, Vol. 21, pp. 20-26, July 1996). Applicants respectfully traverse this rejection.

The Examiner states that **Song** *et al.* teach an isolated nucleic acid primer that is used in allele specific real-time PCR-based genotyping to detect the C3435T polymorphism within human *MDR1* gene where the primer has an additional mismatch at position –3 from the 3' end to abrogate non-specific PCR amplification. The Examiner also states that **Hoffmeyer** *et al.* provide the sequence polymorphism for C3435T within the *MDR1* gene in referring to GenBank M14758 where the C/T mismatch occurs at position 3859. The Examiner further states that **Okimoto** *et al.* exemplify the use of primers containing added mismatches at the –3 position from the 3' end for allele specific PCR and teaches primers with the polymorphism at the 3' terminus that are twenty and twenty-six nucleotides (Table 1).

The Examiner states that the instant SEQ ID NOS: 1 and 2 are identical to nucleotides 3839-3859 without and with the mismatch at 3859. Thus, the Examiner states it would have been *prima facie* obvious to modify **Song** *et al.* to create allele specific primers with a single mismatch at the –3 position from the

3' end for the detection of the *MDR1* C3435T polymorphism. The Examiner contends that one would be motivated to create such a primer by the express teaching of **Song** *et al.* to use the –3 mismatch to abrogate non-specific PCR amplification. The Examiner further contends that the possible –3 mismatch sequences would be obvious variants of one another, including the primers consisting of instant SEQ ID NOS: 1 and 2, and would function as equivalents for the detection of the C3435T polymorphism. Applicants respectfully disagree.

**Song** *et al.* teaches that an additional mismatch to the SNP mismatch at the –3 position from the 3' end of each allele-specific primer for the C3435T SNP abrogates non-specific PCR amplification (Abstract). **Hoffmeyer** *et al.* identifies a cDNA for *MDR1* disclosed in GenBank M14758 which identifies the position of the C3435T SNP within the cDNA at base 3435 (pg. 3475, Table 1).

**Okimoto** *et al.* describe short allele specific primer with a 5' to 3' sequence partially or completely complementary to the 3' to 5' strand of the allele with mismatches at the 3' terminal end and at -2 or-3 from the 3' terminal end or also including additional mismatched bases at the 5' end and/or additional bases added to the 5' end (pg. 21, Table 1). **Okimoto** *et al.* also teach a primer common to both alleles (pg. 21, Table 1). **Okimoto** *et al.* disclose that the inclusion of one or more internal mismatches improves allele specificity and allows amplification of shorter PCR products (pg. 20, 1st PP) and that the allele-specific primers may differ in length from each other (pg. 24, 2nd col.).

Applicants have amended claim 17, as described *supra*, to recite primer pairs with primer sequences of SEQ ID NOS: 1 and 3 and SEQ ID NOS: 2

and 3. SEQ ID NO: 1 and SEQ ID NO: 2 are the primers specific to the wild type and mutant *MDR1* gene and SEQ ID NO: 3 is a primer to a common sequence in both the wild type and mutant gene. Even though **Okimoto** *et al.* teach a primer with a sequence common to both alleles, there is no sequence in M14758 common to both alleles which could result in a primer with SEQ ID NO: 3. One of ordinary skill in the art, although motivated by the combination of prior art, could not arrive at a common primer with SEQ ID NO: 3.

Therefore absent a teaching or suggestion of this claim element in the combination of the prior art, claim 17 is not *prima facie* obvious over **Song** *et al.* in view of **Okimoto** *et al.*, **Hoffmeyer** *et al.*, and GenBank M14758. Accordingly, in view of the claim amendments and arguments presented herein, Applicants respectfully request that the rejection of claim 17 under 35 U.S.C. §103(a) be withdrawn.

Claims 4 and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Song** *et al.* (Clinical Pharmacology & Therapeutics, Vol. 71, No. 2, February 2002, p. P103, abstract WPIII-100) in view of **Hoffmeyer** *et al.* (PNAS, Vol. 97, No. 7, pp. 3473-3478, March 28, 2000), GenBank AC005068 (GI: 10122135, 7 October 2000) and **Okimoto** *et al.* (BioTechniques, Vol. 21, pp. 20-26, July 1996). Applicants respectfully traverse this rejection.

The Examiner states that **Hoffmeyer** *et al.* provide the sequence polymorphism for C3435T within exon 26 of *MDR1* gene in referring to GenBank AC005068 where the C/T mismatch occurs at position 43268 of a sequence that

is complementary to the context sequence in **Hoffmeyer** *et al.* The Examiner further states that **Okimoto** *et al.* teach that an additional mismatch within a primer allows for amplification of "shorter" PCR products (p. 22, 1st col.), e.g., to amplify products between 91 and 163 base pairs (p. 24, 1st col.).

The Examiner states that the instant SEQ ID NOS: 1 and 2 are identical to the complement of nucleotides 43268-43288 without and with the mismatch at 43268 and SEQ ID NO: 3 is identical to nucleotides 43155-43175. Thus, the Examiner states it would have been *prima facie* obvious to modify **Song** *et al.* to create allele specific primers with a single mismatch at the –3 position from the 3' end for the detection of the *MDR1* C3435T polymorphism. The Examiner contends that one would be motivated to create such a primer by the express teaching of **Song** *et al.* to use the –3 mismatch to abrogate non-specific PCR amplification. The Examiner further contends that the possible –3 mismatch sequences would be obvious variants of one another, including the primers consisting of instant SEQ ID NOS: 1, 2 and 3 and would function as equivalents for the detection of the C3435T polymorphism. The Examiner states that for a reverse primer, it would have been obvious to select any primer that would function to amplify DNA with the allele specific primers and that would create "smaller" PCR products, such as primer with SEQ ID NO: 3. The Examiner further notes that the kit of claim 4 encompasses any primers within it that comprise the recited sequences allowing a large degree of variability with regard to even the length of the claimed primers themselves.

**Song** *et al.* and **Okimoto** *et al.* are described *supra*. **Hoffmeyer** *et al.* identifies a cDNA for exons 8-28 of *MDR1* disclosed in GenBank AC005068 (pg. 3474, col. 1, last PP) which identifies the position of the C3435T SNP within the cDNA at nucleotide 43268. Applicants' invention, as recited in amended claims 4 and 17, is as described *supra*.

As amended, claims 4 and 17 are drawn to primer pairs of an allele-specific primer SEQ ID NO: 1 with common primer SEQ ID NO: 3 and allele-specific primer SEQ ID NO: 2 with common primer SEQ ID NO: 3. It appears to the Applicants that the Examiners' statements that SEQ ID NOS: 1 and 2 are identical to the complement of nucleotides 43268-43288 without and with the mismatch at 43268 and SEQ ID NO: 3 is identical to nucleotides 43155-43175 and that given the teachings in the prior art it or what is known in the art it would be obvious for one of ordinary skill in the art to design the instant allele-specific and common primers is hindsight.

**Okimoto** *et al.* teach a 20 bp primer with the required mismatches. **Okimoto** also teaches that allele specific primers may be longer if additional mismatched 5' bases are added and/or a mismatch is incorporated within the 5' end of the primer at the junction between the 5' mismatch and the 5' extension. **Song** *et al.* teach an additional –3 mismatch from the 3' end abrogates non-specific PCR amplification. **Okimoto** teach that the additional 5' mismatch or extension improves upon this. Thus, presented with this combination of prior art, the motivation to one of ordinary skill in the art would be to find the best allele specific primers for the C/T SNP which might include the additional 5' changes.

One of ordinary skill in the art would not know without trying which has long been held not to be the standard under 35 U.S.C. §103(a).

In considering Applicants' SEQ ID NO: 3, **Okimoto** *et al.* just teach a common primer sequence. The common primer sequence has no distinguishing features other than the sequence is common to both wildtype and mutant alleles and that short PCR products of 91-163 bp can be generated. As the Examiner stated, any sequence common to both alleles and effective to generate the short PCR products would work, but it is not obvious that one of ordinary skill in the would recognize Applicants SEQ ID NO: 3 as effective to work in this particular genotyping application simply by knowing the sequence of the *MDR1* gene. Even though **Okimoto** *et al.* produced PCR amplicons within a 91-163 bp range, thereby suggesting a region of DNA from which to design a common primer, one of ordinary skill in the art is still reduced to trying various sequences from within this range; it is not inherently obvious that SEQ ID NO: 3 would work. The guidance from the prior art to one skilled in the art is minimal. The common primer is short in length, **Okimoto** *et al.* teaches 23 nucleotides. The shorter the primer the less specific it is and the greater the chance of non-specific binding elsewhere within the gene, particularly with a total genomic sequence of almost 100,000 bp in AC005068. In addition the primer sequence would have to be one that didn't form dimers or other structures. One of ordinary skill in the art again would be trying.

Furthermore, assuming *arguendo*, the combination of the prior art references may provide motivation to one of ordinary skill in the art to try to design

primers using the 3' terminal mismatch and a –3 from 3' terminal end internal mismatch, it is not obvious that any primer having these particular mismatches would function equivalently. Because these are short primers, the addition or deletion of a single base could effect the stability of the primer. Also, the –3 mismatch itself must not be too destabilising within a specific sequence or the PCR reaction will fail. So any variant primer is not necessarily functionally equivalent. To reiterate one of ordinary skill in the art must simply try various primer sequences which is not the standard for obviousness.

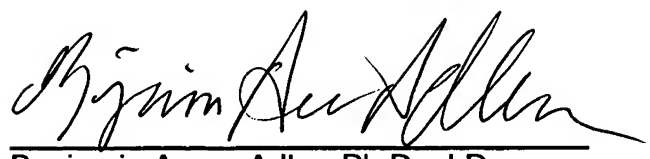
Obvious to try has long been held not to be the standard for obviousness under 35 U.S.C. 103(a). Thus, **Song** *et al.* in view of **Okimoto** *et al.*, **Hoffmeyer** *et al.*, and GenBank AC005068 cannot render claims 4 and 17 *prima facie* obvious. Applicants submit that if the primer pairs of amended claim 17 are not obvious, then a kit containing these primer pairs also is not obvious. Accordingly, in view of the amendment and arguments presented herein, Applicants respectfully request that the rejection of claims 4 and 17 under 35 U.S.C. 103(a) be withdrawn.

This is intended to be a complete response to the Office Action, mailed March 28, 2005. Applicants submit that pending claims 4 and 17 are in condition for allowance. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Applicant encloses a Petition for a Two Month Extension of Time. Please credit the $225 petition fee under 37 C.F.R. 1.17(a) to the credit card identified on the Form PTO-2038. In the absence of this form, please debit

any fees due from Deposit Account 07-1185 upon which Applicant's counsel is allowed to draw.

Respectfully submitted,

Date: Aug 16, 2005



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